Review of patient inclusion exclusion criteria

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Consulting

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Editorial

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American Diabetes Association.
Cure • Care • Commitment

Enrollment criteria and validity in clinical trials

- *Internal validity* asks the question does the treatment work in a defined population (efficacy).
  - The protocol controls all important variables so only the intervention can impact outcomes.

- *External validity* asks the question are the results generalizable: to what populations, settings, treatment variables, and measurement variables can this effect be generalized. (Campbell and Stanely 1966)

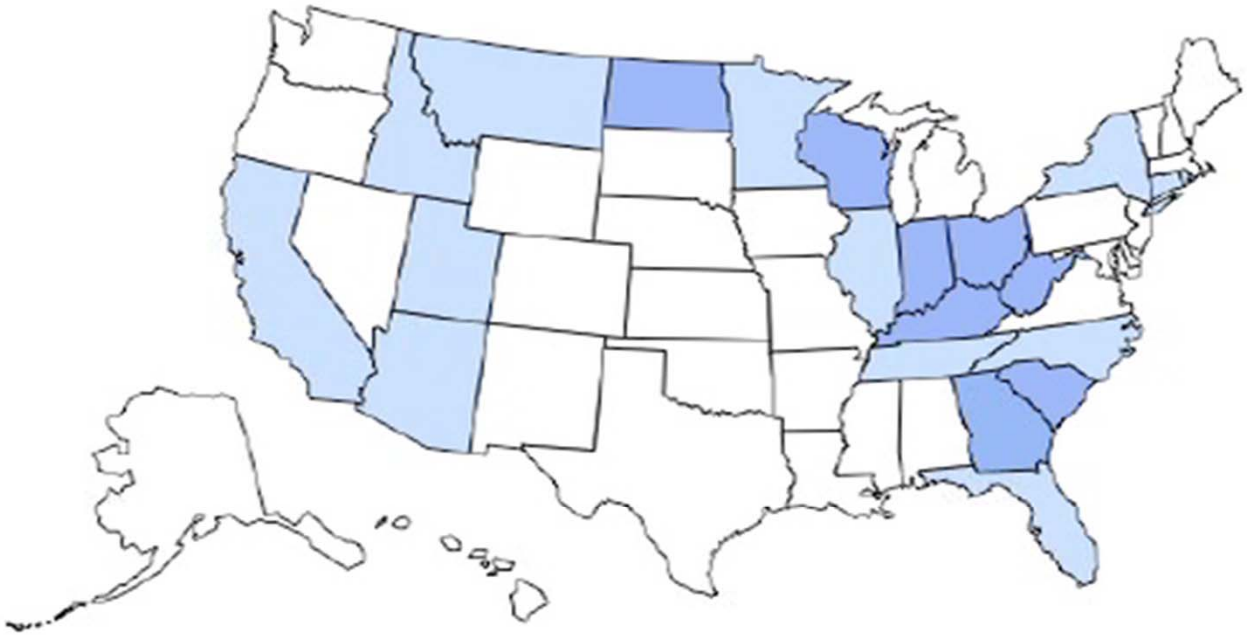
Diabetic Distal Symmetric Polyneuropathy

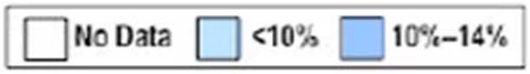
- Most common, costly and disabling microvascular complication of diabetes mellitus.
- Over $3 Billion in direct health system costs in 2003.
- Leading cause for ulceration and amputation.

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)





Source: Behavioral Risk Factor Surveillance System, CDC.

Clinical Trials for DSP

- Reversible metabolic injury seques into irreversible axon loss – thus trials should include patients with early disease (e.g. preserved sural sensory responses).

- Exclude patients with potentially confounding comorbidities (internal validity).

- Endpoints – clinical scales, nerve conduction studies or composites.

Challenges in Design of Multicenter Trials

End points assessed longitudinally for change and monotonicity

Assessed clinimetric performance of DSP endpoints in placebo arms of Nathan 1, 2 Lilly protocols, and Rochester Diabetic Neuropathy Cohort

- Clinical scales and symptoms improve
- Subtle monontonic decline in sural amplitude and peroneal motor conduction velocity.
- No progression in other endpoints.
- Measurement “noise” in many endpoints.

Dyck PJ, Norell JE, Tritschler H, et al. Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity. Diabetes Care. 2007(null) ed. 2007 Oct;30(10):2619–25.

Efficacy and Safety of Antioxidant Treatment With α-Lipoic Acid Over 4 Years in Diabetic Polyneuropathy

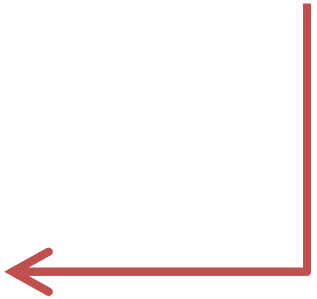
The NATHAN 1 trial

- 4 year RCT of 600mg ALA vs. placebo.
- Primary endpoint NIS-LL + 7 neurophysiologic tests.
- There was no decline in primary endpoint (NCS stable), and no treatment efficacy.
- There was improvement in NIS-LL

The Therapeutic Conundrum of Diabetic Neuropathy

Advanced Neuropathy is Difficult or Impossible to Reverse

Treatment Trials Must Focus on Early Neuropathy (e.g. preserved Sural responses)



Early Neuropathy Progresses Slowly and Traditional Surrogate Endpoints (NCS) Do Not Change

How can we test treatments when the disease doesn't change at the stage at which it is amenable to therapy?

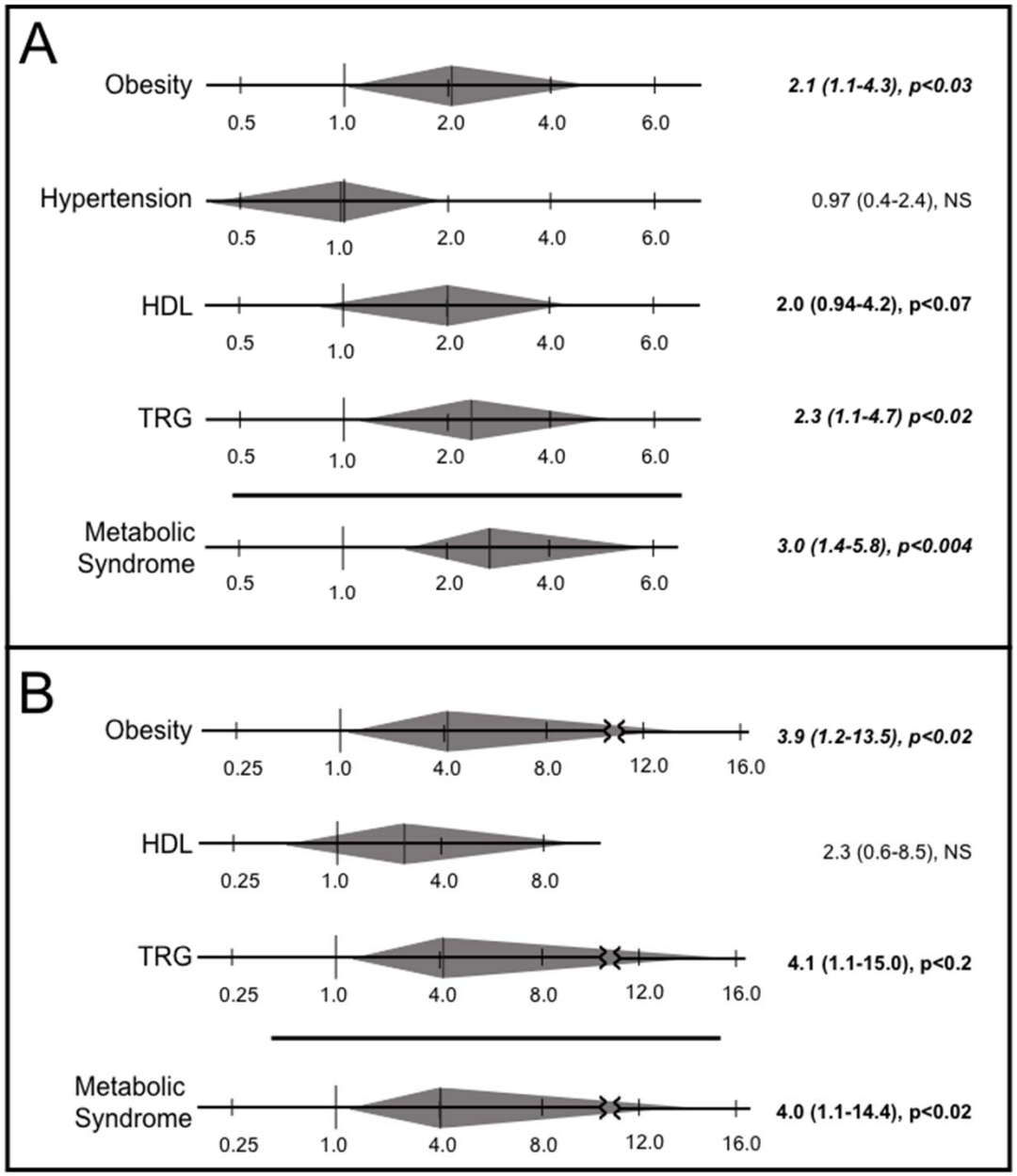
An unintended consequence of maximizing internal validity . . .

Challenges in Design of Multicenter Trials

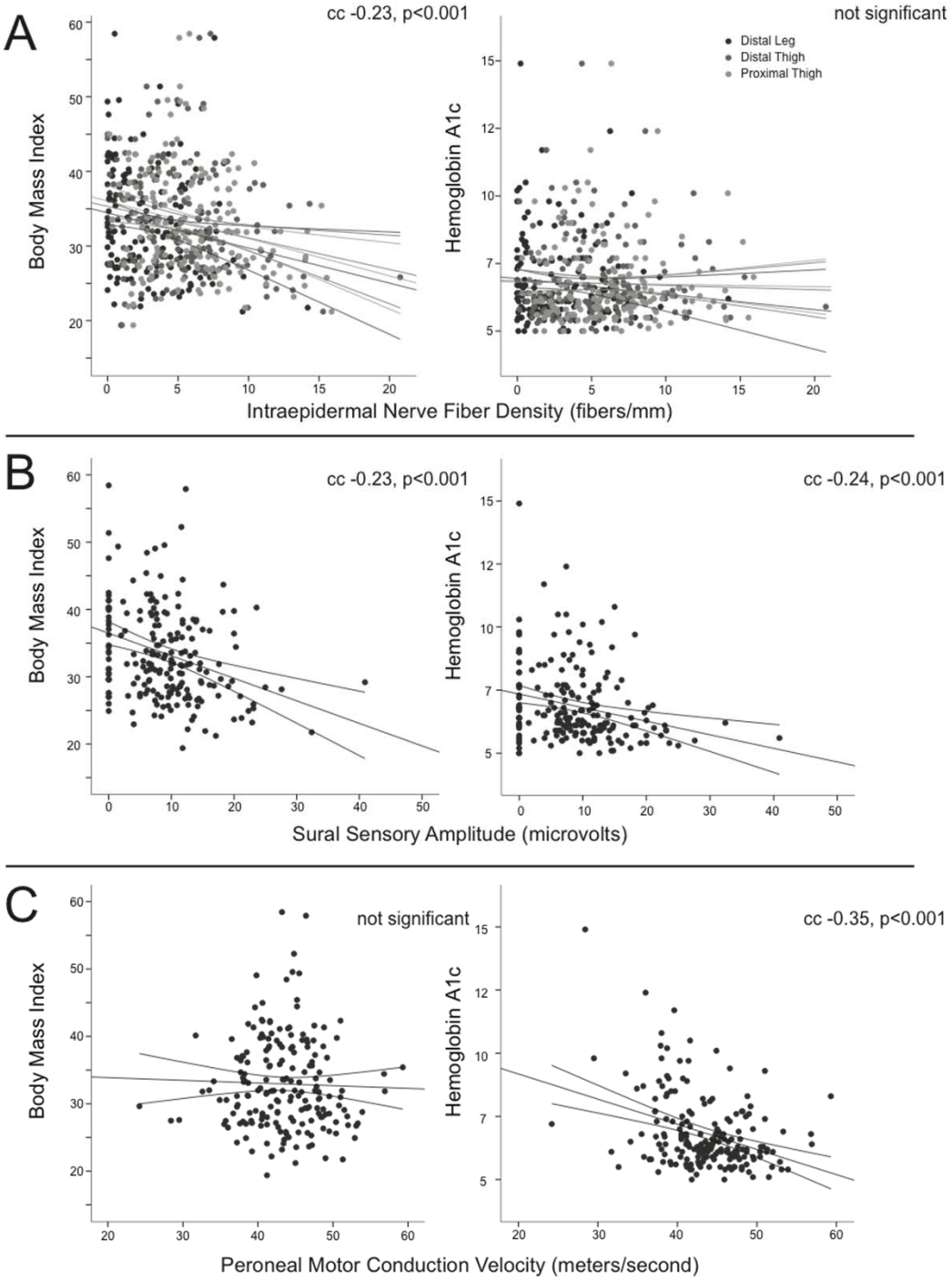
End points assessed longitudinally for change and monotonicity

1. Recruit patients with developing rather than established neuropathy – *need new endpoints or trial designs.*
2. Focus on type 1 patients –*internal validity.*
3. Select patients who cannot or will not achieve glycemic control – *ethical issues, internal validity*
4. Select endpoints known to show monotonic worsening – *need new endpoints to achieve this practically.*
5. Restricted numbers of centers and examiners –*internal validity.*

Dyck PJ, Norell JE, Tritschler H, et al. Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity. Diabetes Care. 2007(null) ed. 2007 Oct;30(10):2619–25.



Smith AG, Singleton JR. Obesity hyperlipidemia and metabolic syndrome are risk factors for early diabetic neuropathy. Journal of Diabetes and Its Complications. :InPress.



Smith AG, Singleton JR. Obesity hyperlipidemia and metabolic syndrome are risk factors for early diabetic neuropathy. Journal of Diabetes and Its Complications. :InPress.

Diabetic Retinopathy (DR) Screening

14,554 patients with no DR or mild DR at two consecutive annual screenings.

1. No DR at either visit: 7246 - 120 progressed to sight threatening DR (STDR) (0.7%year)
2. No DR at first, 1 eye at second: 1778 - 80 progressed to STDR (1.9%/year)
3. DR in both eyes each year: 1159 -299 progressed (11%/yr), hazard ratio of 18.2 (14.7-22.5).

Stratton IM, Aldington SJ, Taylor DJ, Adler AI, Scanlon PH. A Simple Risk Stratification for Time to Development of Sight-Threatening Diabetic Retinopathy. Diabetes Care. 2012 Nov.

Early (Developing) DPN is Characterized by Progressive Small Fiber (but not large fiber) Loss

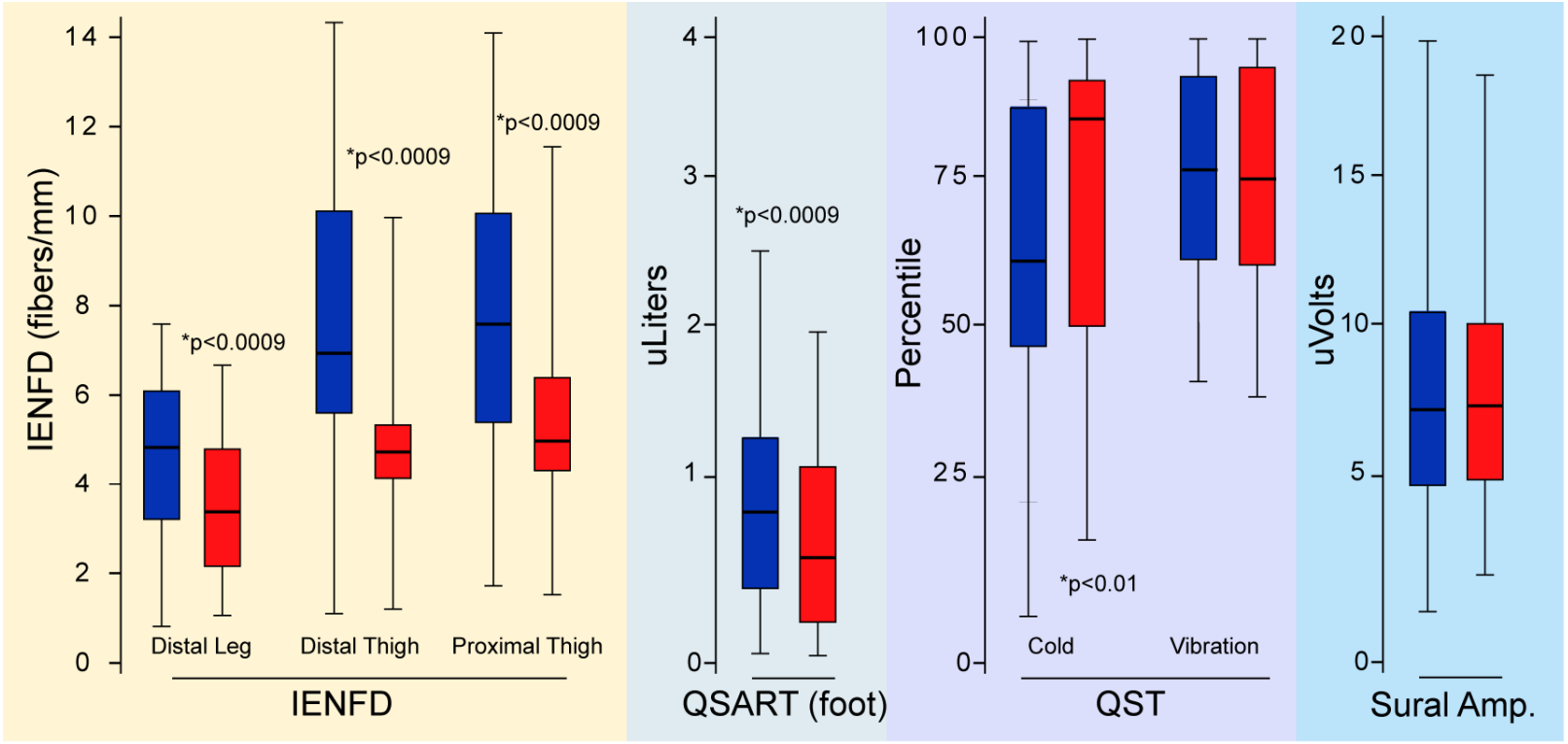
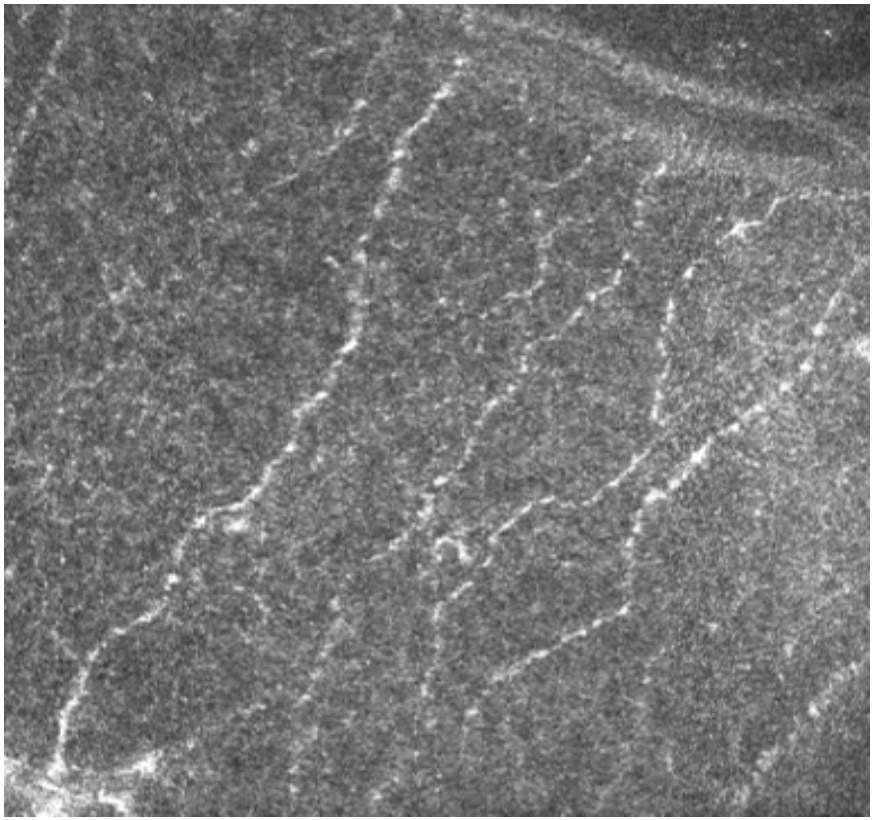


Figure 3. Sensory axonal function declined significantly over 24 months, particulary measures specific for small fiber inegrity. (A) IENFD declined at all sites: distal leg 4.1 +/- 2.9 to 2.6 +/-2.1 ($p<0.0009$), distal thigh 7.2 +/- 3.6 to 4.3 +/- 2.1 ($p<0.0009$) , and proximal thigh 7.7 +/-3.2 to 5.0 +/- 2.6 ($p<0.0009$). (C) Sweat volume at the distal leg decreased from 0.99 +/- 0.77 uL to 0.58 +/- 0.63 uL ($p<0.0009$). (C)Cold detection threshold (CDT) increased from 66 +/- 27% to 74 +/- 27% ($p<0.01$). There was no change in vibration detection threshold. (D) Nerve conduction parameters such as sural sensory amplitude did not change.



Smith AG, Kim G, Porzio M, et al. Corneal confocal microscopy is efficient well tolerated and reproducible. Journal of the Peripheral nervous system : JPNS. In Press.

Challenges to External Validity

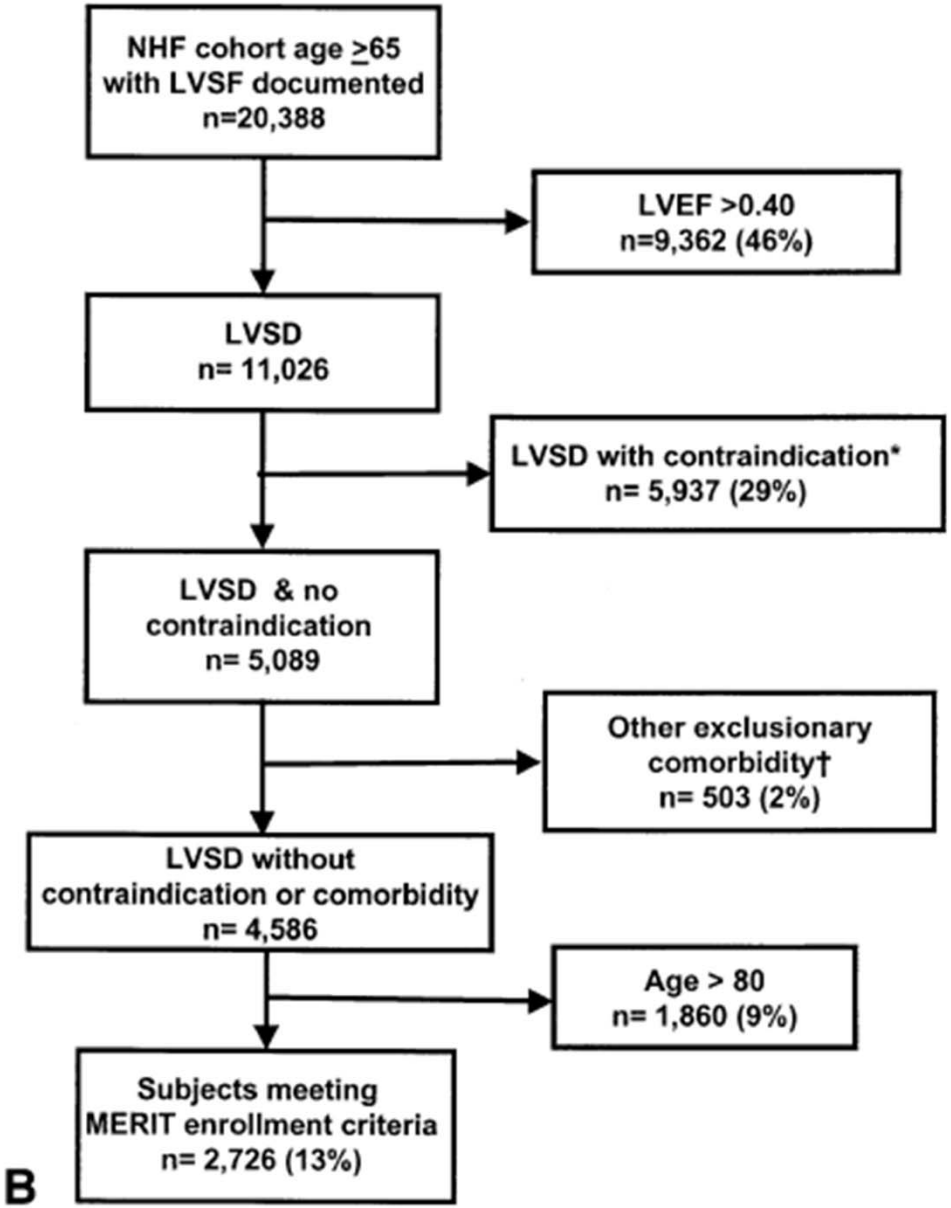
- Limited patient access to trial centers
- Selection bias
- Physician and patient resistance/preference to randomization of participants to a specific arm.
- Overly rigorous inclusion exclusion

Table I. Enrollment criteria of clinical trials used for this analysis

Trial	Inclusions	Exclusions
SOLVD	Left ventricular ejection fraction ≤0.35	Drug-specific Moderate or severe aortic stenosis Unstable angina* Recent acute myocardial infarction Serum creatinine >2.0 mg/dL Prior intolerance of angiotensin-converting enzyme inhibitors General Age >80 years Other exclusionary comorbidity†
MERIT-HF	Left ventricular ejection fraction ≤0.40 New York Heart Association functional class II-IV	Drug-specific Unstable angina* Recent acute MI Heart failure secondary to alcoholism or other systemic disease* Heart transplantation* Chronic lung disease or asthma General Age > 80 years Other exclusionary comorbidity†
RALES	Left ventricular ejection fraction ≤ 0.35 New York Heart Association functional class III-IV	Drug-specific Moderate or severe aortic stenosis Other significant valvular heart disease* Congenital heart disease* Heart transplantation* Unstable angina* Serum potassium >5.0 mmol/L Serum creatinine >2.5 mg/dL General Other exclusionary comorbidity†

*Ascertained by secondary diagnosis ICD-9 code(s).
†Dementia, metastatic malignancy, or hepatic failure.

Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J. 2003 Aug;146(2):250–7.



*COPD, asthma, secondary cardiomyopathy, unstable angina, acute MI (current episode of care), 2nd or 3rd degree AV block, or heart transplantation

†Dementia, metastatic malignancy, or hepatic failure

- Less than 1/5 met entrance criteria.
- Elderly and women relatively excluded.
- Comborbidities
- Failure to meet severity definition.

Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J. 2003 Aug;146(2):250–7.

Classification of Exclusion Criteria

Poorly Justified Reasons for Exclusion:

Any of the following unless the condition or intervention is specific to the criterion, or the criterion has a direct bearing on condition/intervention/results

- Age
- Sex or sex specific conditions
- Race/ethnicity or language
- Educational background
- Socioeconomic status
- Cognitive ability
- Physical disability
- Chronic health condition
- Placebo or intervention would be harmful
- Lack of equipoise (intervention harmful)
- Effect of intervention difficult to interpret

Strongly Justified Reasons for Exclusion:

- Unable to provide informed consent
- Placebo or intervention would be harmful
- Lack of equipoise (intervention harmful)
- Effect of intervention difficult to interpret

Potentially Justified Reasons for Exclusion:

- Is neither a strongly justified reason nor a poorly justified reason.
- Individual may not adhere.
- Individual may not complete follow up.

1. Van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007 Mar 21;297(11):1233–40.

MEDLINE search for RCT's 1994-2006 in general medical journals with high impact factors. Identified 4827 articles, 283 selected using a series technique.

Table 3. Justification of Exclusion Criteria

	No. (%) of Trials*
Grading of individual exclusion criteria	
Total number of exclusions	2709 (100.0)
Strongly justified	1275 (47.2)
Potentially justified	430 (15.9)
Poorly justified	1004 (37.1)
At least 1 poorly justified exclusion criterion	238 (84.1)
Category with poor justification	
Age	160 (78.4)
Medical comorbidity	149 (64.8)
Sex	70 (52.6)
Females	69 (62.2)
Males	1 (4.5)
Medication-related	56 (36.6)
Socioeconomic status	31 (79.5)
Percentage of poorly justified exclusion criteria	
≥10	228 (80.6)
≥25	174 (61.5)
≥50	83 (29.3)
≥75	24 (8.5)
Exclusions per trial, mean (SD)	9.5 (6.1)

*Unless otherwise indicated.

Table 4. Independent Associations Among Trial Characteristics and Number of Exclusion Criteria

	RR (95% CI)	*P* Value
Type of trial		
Drug intervention	1.35 (1.11-1.65)*	.003
Multicenter	1.26 (1.06-1.52)	.009
Medical condition	1.07 (0.87-1.33)	.48
Trial characteristic		
Industry sponsorship	0.93 (0.78-1.11)	.39
Trial quality score	1.05 (0.99-1.07)	.08
University origin	0.98 (0.80-1.19)	.85
Trial size	0.99 (0.99-1.00)	.08

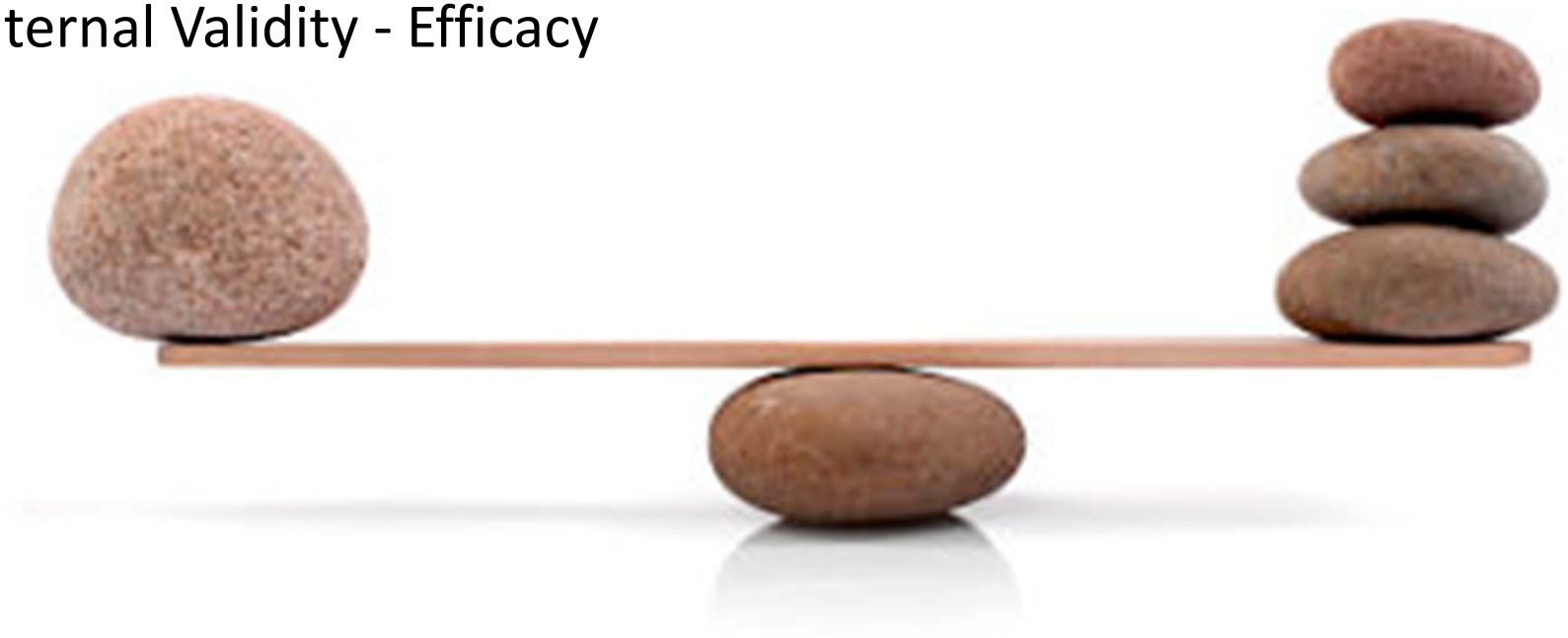
Abbreviations: CI, confidence interval; RR, risk ratio.
*Drug intervention trials have 35% more exclusions than trials without drug interventions.

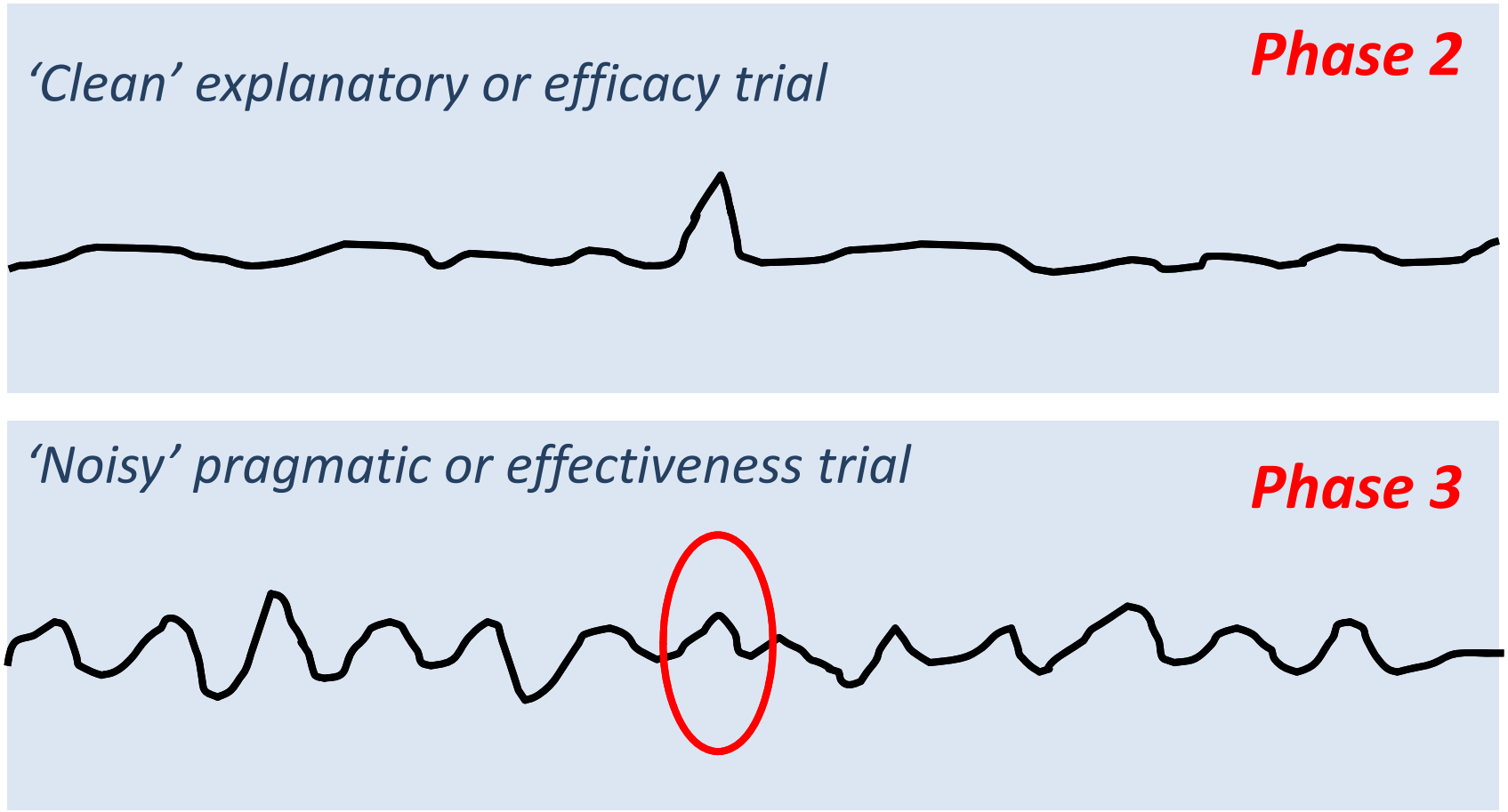
Table 7. Associations Among Exclusion Criteria and Industry-Sponsored Trials

	Specific Exclusions		Poorly Justified Exclusions	
Exclusion Criteria	χ^2	*P* Value	χ^2	*P* Value
Medication-related	13.5	<.001	11.4	<.001
Medical comorbidity	10.9	.001	5.8	.01
Female sex	3.6	.06	0.01	.94
Socioeconomic status	3.6	.06	0.8	.38
Age	3.9	.05	0.1	.73

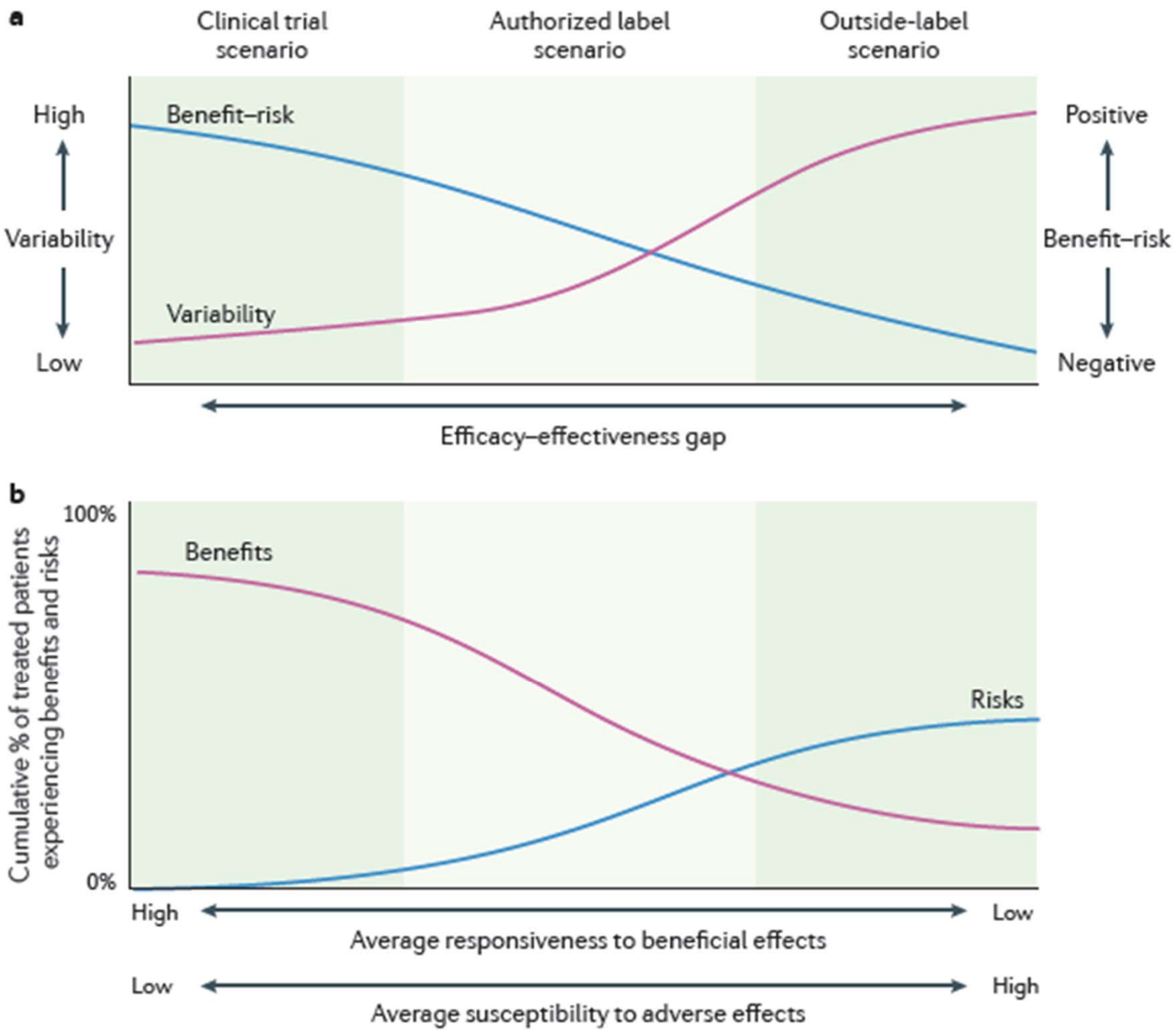
External Validity - Effectiveness

Internal Validity - Efficacy

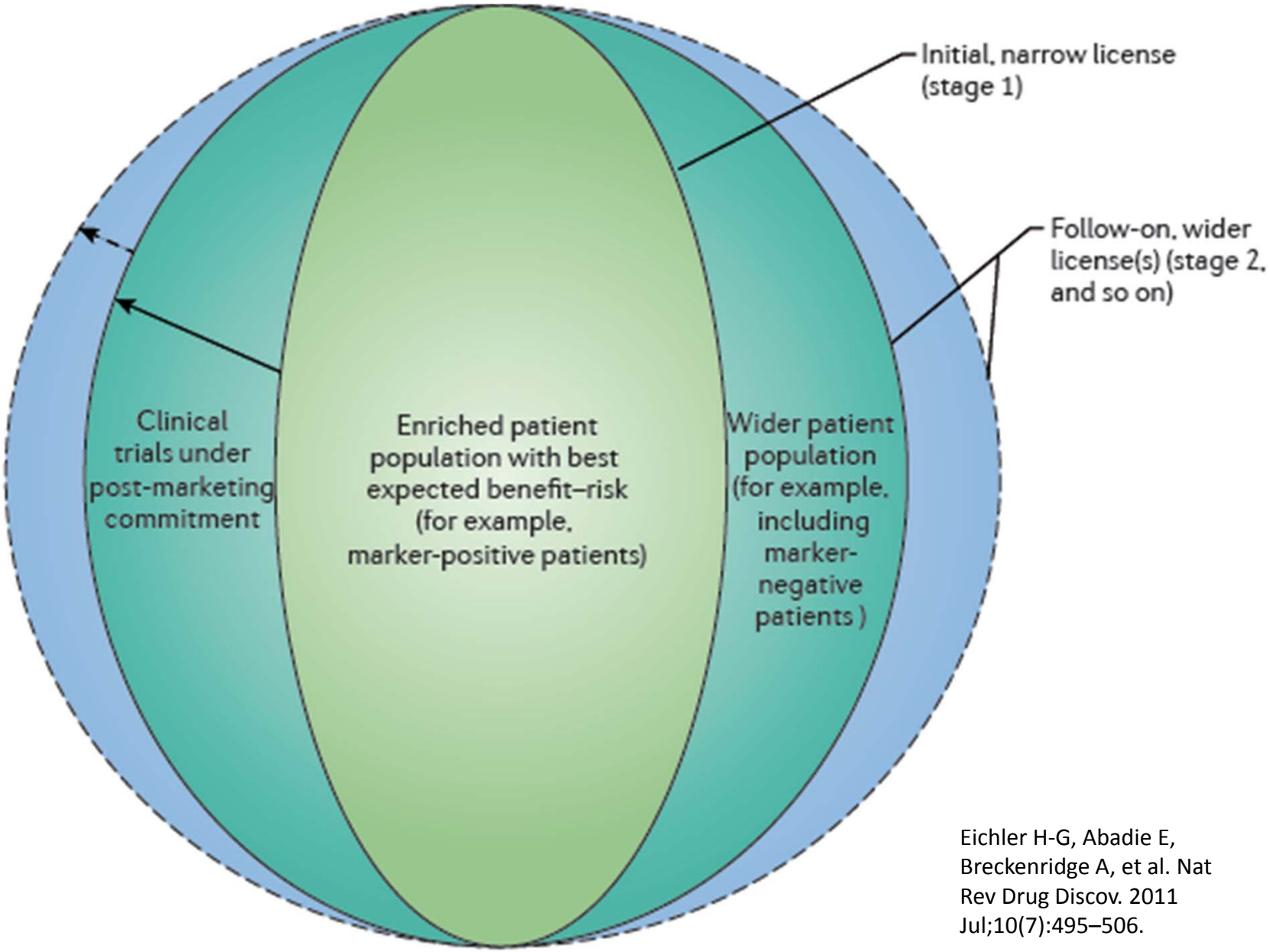




Eichler H-G, Abadie E, Breckenridge A, et al. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. Nat Rev Drug Discov. 2011 Jul;10(7):495–506.


a
Clinical trial scenario
Authorized label scenario
Outside-label scenario
High
Variability
Low
Benefit–risk
Variability
Positive
Benefit–risk
Negative
Efficacy–effectiveness gap
b
Cumulative % of treated patients experiencing benefits and risks
100%
0%
Benefits
Risks
High
Low
Average responsiveness to beneficial effects
Low
High
Average susceptibility to adverse effects

The “Onion Skin” Model of Drug Licensing



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Recruitment is hard . . .

- HIPAA and IRB make it more difficult and costly to recruit participants and identify representative samples.
- Poor accrual is one of the most common causes for clinical trial failure.

Conflict of interest and bias in clinical trials

- Clinical trials are increasingly performed outside of academic centers.
- Enrollment based payment (“per patient budgeting”).
- Central pressure to fully enroll studies.
- Aggressive recruitment techniques.
- Patients are busy, need for reimbursement
  - Professional study subjects


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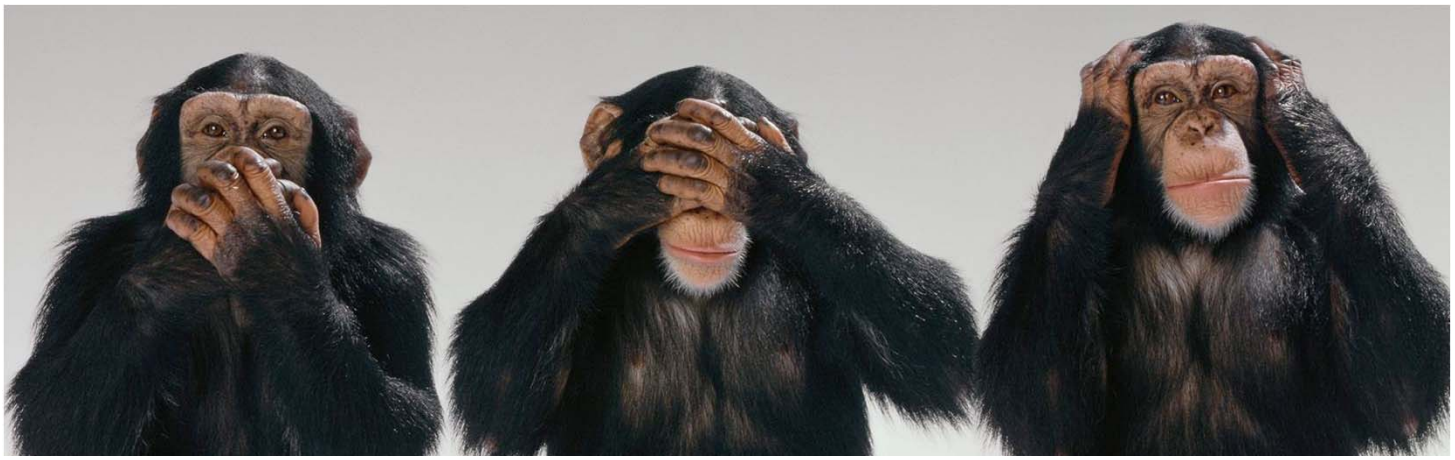
Resulting in . . .

- Bias – poor external validity because patients are not representative.
- Conflict of interest – both organizational/macroeconomic and individual/microeconomic (investigator)



Recommendations:

1. RCT need to recruit a diverse population including women and the elderly.
2. Enrollment criteria must be explicitly spelled out and justified – CONSORT.
3. For slowly progressive neuropathies, maximize internal validity by identifying at risk populations (new endpoints).
   - Screening for patients with transitional neuropathy or high risk of incident DPN.
4. Onion skin model. Focused approval with post approval effectiveness studies. Leverage EMR.
5. Enhance funding for effectiveness research (PCORI)
6. Recognition of COI and avoidance of recruitment based PI reimbursement. Neutral arbiter of enrollment criteria.